

## Supplementary Material

### Intrinsic (gas-phase) acidity and basicity of paracetamol

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**Dedicated to Professor Rosa Maria Claramunt on the occasion of her 65<sup>th</sup> birthday**

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**Table S1.** Gas-phase thermochemical quantities of reference used to determine the acidity and basicity of paracetamol <sup>a</sup>

Reference acids, A <sub>ref(i)</sub> H		GA, kJ·mol <sup>-1</sup>	Δ <sub>acid</sub> H <sup>0</sup> , kJ·mol <sup>-1</sup>	Δ <sub>acid</sub> S <sup>0</sup> , J·mol <sup>-1</sup> ·K <sup>-1</sup>
i=1	2,3,5,6-tetramethylbenzoic acid	1388.4 ± 8.4	1417.7 ± 8.8	98.4
i=2	2,2,2-trifluoroacetamide	1409.8 ± 8.4	1439.1 ± 8.8	98.4
i=3	Trimethylacetic acid	1413.5 ± 8.4	1442.8 ± 8.8	98.4
i=4	Isobutyric acid	1419.4 ± 8.4	1448.7 ± 8.8	98.4
Average		1407.8 ± 8.4 <sup>b</sup>	1437.1 ± 8.8 <sup>b</sup>	98.4 ± 8.4 <sup>c</sup>
Reference bases, B <sub>ref(i)</sub>		GB, kJ·mol <sup>-1</sup>	PA, kJ·mol <sup>-1</sup>	Δ <sub>p</sub> S <sup>0</sup> , J·mol <sup>-1</sup> ·K <sup>-1</sup>
i=1	1,2,3-triazole	856.7	886.8	101.2
i=2	Pyrazole	861.3	894.8	112.4
i=3	3-methylpyrazole	874.7	906.5	106.8
i=4	Benzylamine	880.1	914.0	113.8
Average		868.2 ± 8.4 <sup>b</sup>	900.5 ± 8.4 <sup>b</sup>	108.5 ± 8.4 <sup>c</sup>

<sup>a</sup> Taking from NIST Chemistry Webbook, NIST Standard Reference Database, <http://webbook.nist.gov>. <sup>b</sup> Since uncorrelated uncertainty with weighting factor (equals to 1/s<sub>i</sub><sup>2</sup> where s<sub>i</sub> = uncertainty experimental of i-datum) is almost ± 4 kJ·mol<sup>-1</sup> while standard deviation is ± 13.5 kJ·mol<sup>-1</sup>, we decided to consider 8.4 (8.8) kJ·mol<sup>-1</sup> [or 2 (2.1) kcal/mol] as accuracy of this average value, in accordance with the recommendations of NIST. <sup>c</sup> It is assumed to have ± 8.4 J·mol<sup>-1</sup>·K<sup>-1</sup> (or 2 cal/mol K) uncertainty.

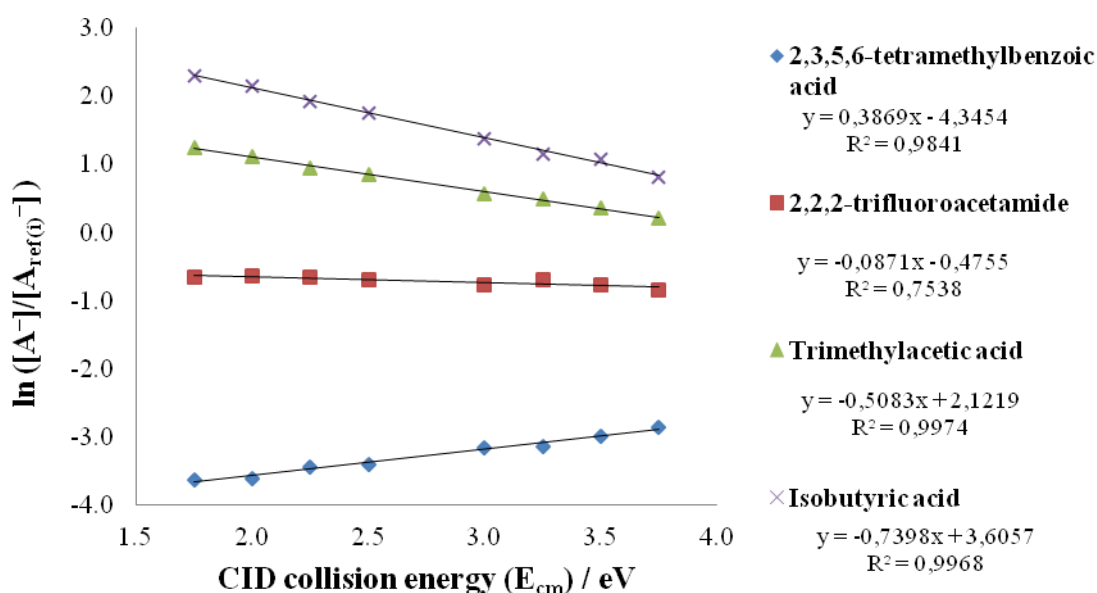
**Table S2.** Experimental ESI conditions

Nebulizing gas (Air)		Drying gas		Potential, keV
Reference acids	Pressure, psi	Temperature, °C	Pressure, psi	Needle
1	10	200	10	-2.9
2	10	175	10	-3.7
3	15	225	10	-3.2
4	15	225	10	-3.3
Nebulizing gas (N <sub>2</sub> )		Drying gas		Potential, keV
Reference basics	Pressure, psi	Temperature, °C	Pressure, psi	Needle
1	15	225	10	3.5
2	15	150	10	3.8
3	15	175	15	3.5
4	15	200	10	3.3

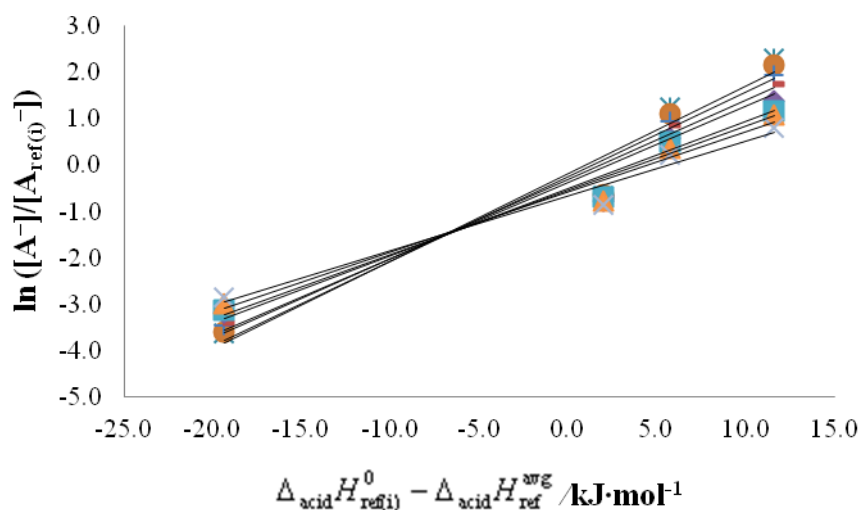
## 1. Determination of Gas-Phase acidity of paracetamol

**Table S3.** Values of  $\ln([A^-]/[A_{\text{ref}(i)}^-])$  of CID products of heterodimer  $[A\cdot H\cdot A_{\text{ref}(i)}]^-$  of paracetamol and four reference acids, obtained at different collision center of mass - energies  $E_{\text{cm}}$

$E_{\text{cm}}/\text{eV}$	$\ln([A^-]/[A_{\text{ref}(i)}^-])$							
	1.75	2.00	2.25	2.50	3.00	3.25	3.50	3.75
$A_{\text{ref}(i)} = \mathbf{1}$	-3.629	-3.607	-3.445	-3.415	-3.172	-3.136	-2.993	-2.855
<b>2</b>	-0.650	-0.642	-0.655	-0.701	-0.766	-0.691	-0.762	-0.853
<b>3</b>	1.248	1.111	0.951	0.855	0.569	0.495	0.351	0.212
<b>4</b>	2.307	2.152	1.931	1.746	1.383	1.159	1.077	0.815



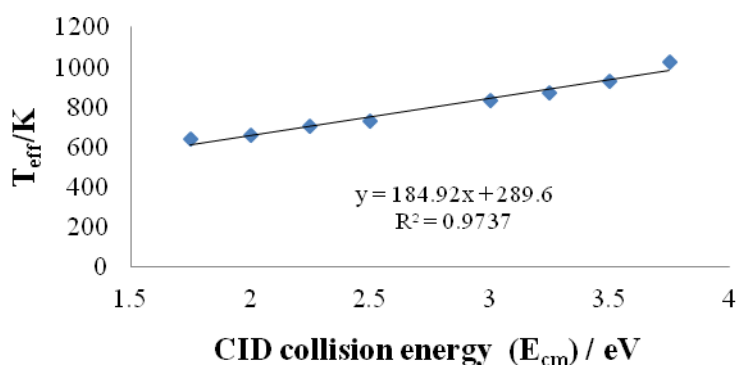
**Figure S1.** Plots of  $\ln([A^-]/[A_{\text{ref}(i)}^-])$  of CID products of heterodimer  $[A\cdot H\cdot A_{\text{ref}(i)}]^-$  vs collision center of mass energies,  $E_{\text{cm}}$



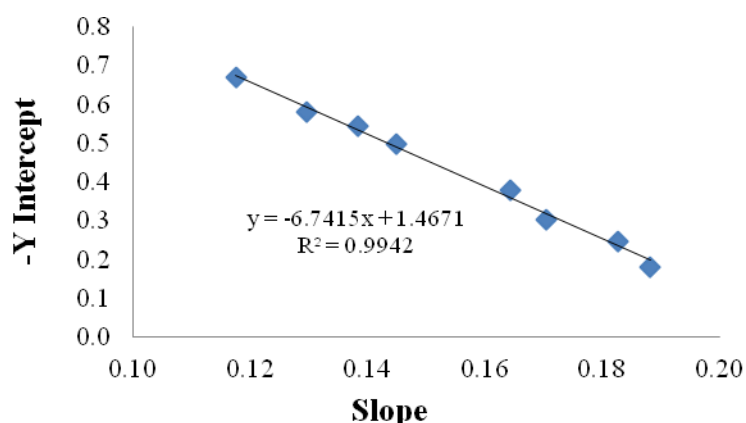
**Figure S2.** (a) Plots of  $\ln([A^-]/[A_{\text{ref}(i)}^-])$  vs  $(\Delta_{\text{acid}} H_{\text{ref}(i)}^0 - \Delta_{\text{acid}} H_{\text{ref}}^{\text{avg}})$  from dissociation of  $[A \cdot H \cdot A_{\text{ref}(i)}]^-$  at eight  $E_{\text{cm}}$  collision energies.

**Table S4.** Values of the linear-fits obtained from data depicted in Figure S2

$E_{\text{cm}}/\text{eV}$	1.75	2.00	2.25	2.50	3.00	3.25	3.50	3.75
<b>Slope</b>	0.188	0.183	0.171	0.164	0.145	0.138	0.130	0.117
<b>Y-intercept</b>	-0.181	-0.246	-0.305	-0.379	-0.496	-0.543	-0.582	-0.670
<b>R<sup>2</sup></b>	0.953	0.959	0.961	0.963	0.965	0.976	0.973	0.969
<b>T<sub>eff</sub>/K</b>	639.0	658.3	705.1	731.5	830.5	869.6	927.3	1023.7



**Figure S3.** Plots of “effective temperature”  $T_{\text{eff}}$  against CID energies,  $E_{\text{cm}}$ .



**Figure S4.** Plot of “-Y intercept” against “slope” values consigned in Table S4.

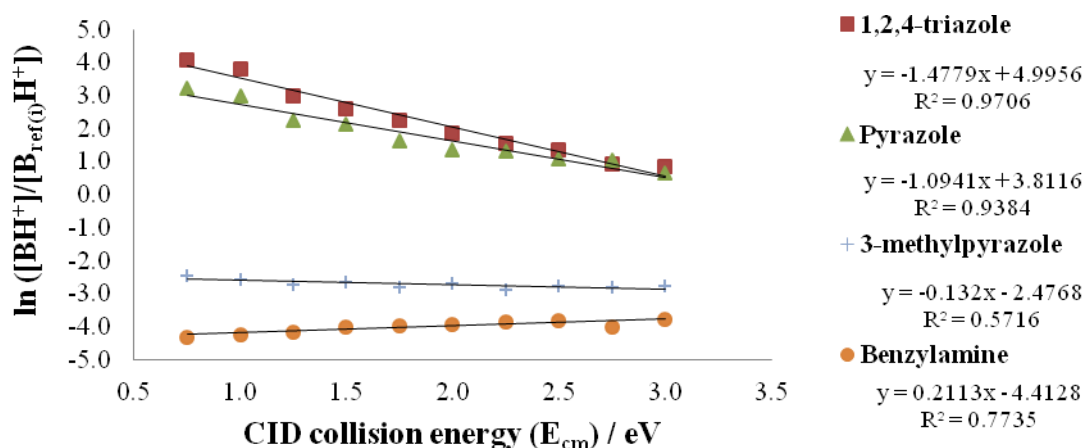
**Table S5.** Experimental deprotonation enthalpy  $\Delta_{\text{acid}}H^0$ , deprotonation entropy  $\Delta_{\text{acid}}S^0$  and acidity GA of paracetamol

$\Delta_{\text{acid}}H^0$ , $\text{kJ}\cdot\text{mol}^{-1}$	$\Delta_{\text{acid}}S^0$ , $\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$	$\Delta_{\text{acid}}G^0 = GA$ , $\text{kJ}\cdot\text{mol}^{-1}$
$1430.3 \pm 8.8$	$86.2 \pm 8.4$	$1404.7 \pm 8.8$

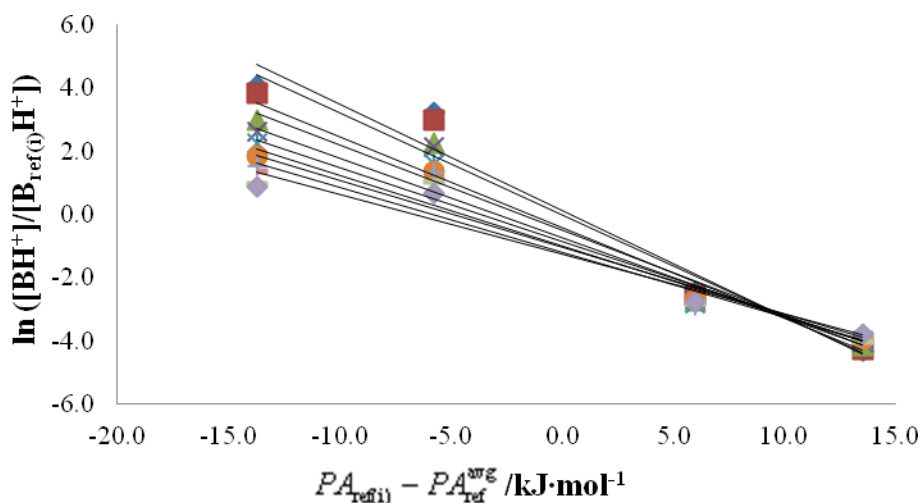
## 2. Determination of Gas-Phase basicity of paracetamol

**Table S6.** Values of  $\ln([\text{BH}^+]/[\text{B}_{\text{ref}(i)}\text{H}^+])$  of CID products of heterodimer  $[\text{B}-\text{H}-\text{B}_{\text{ref}(i)}]^+$  of paracetamol and four reference bases, obtained at different collision center of mass - energies  $E_{\text{cm}}$

$E_{\text{cm}}/\text{eV}$ $\text{B}_{\text{ref}(i)}$	$\ln([\text{BH}^+]/[\text{B}_{\text{ref}(i)}\text{H}^+])$									
	0.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.00
<b>i = 1</b>	4.071	3.811	2.994	2.612	2.238	1.856	1.525	1.350	0.938	0.849
<b>2</b>	3.231	2.973	2.238	2.113	1.602	1.356	1.297	1.094	1.050	0.646
<b>3</b>	-2.446	-2.592	-2.743	-2.659	-2.812	-2.702	-2.910	-2.769	-2.820	-2.789
<b>4</b>	-4.319	-4.254	-4.167	-4.014	-3.979	-3.957	-3.858	-3.816	-4.025	-3.778



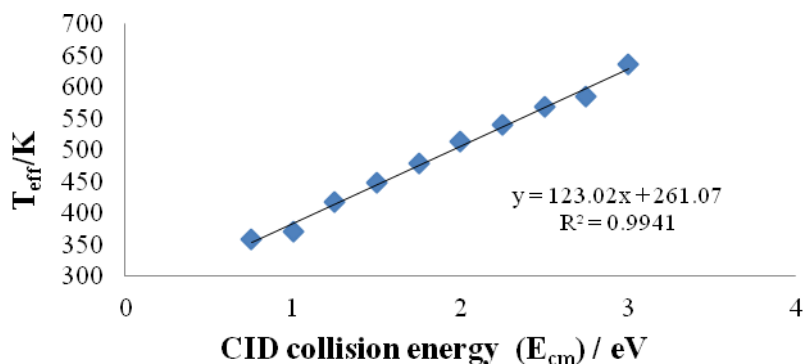
**Figure S5.** Plots of  $\ln([BH^+]/[B_{ref(i)}H^+])$  of CID products of heterodimer  $[B \cdot H \cdot B_{ref(i)}]^+$  vs collision center of mass energies  $E_{cm}$ .



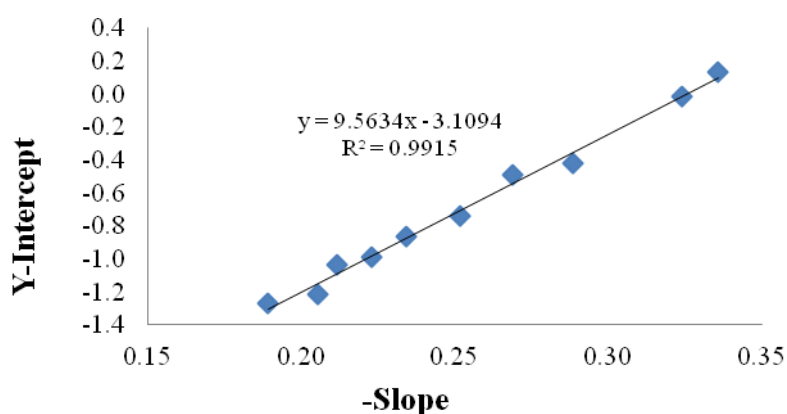
**Figure S6:** (a) Plots of  $\ln([BH^+]/[B_{ref(i)}H^+])$  vs  $(PA_{ref(i)} - PA_{ref}^{avg})$  from dissociation of  $[B \cdot H \cdot B_{ref(i)}]^+$  at ten  $E_{cm}$  collision energies.

**Table S7.** Values of the linear-fits obtained from data depicted in Figure S6

$E_{cm}/eV$	0.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.00
<b>Slope</b>	-0.336	-0.324	-0.288	-0.269	-0.251	-0.234	-0.223	-0.211	-0.205	-0.189
<b>Y-intercept</b>	0.134	-0.016	-0.419	-0.487	-0.738	-0.862	-0.987	-1.035	-1.214	-1.268
<b>R<sup>2</sup></b>	0.959	0.957	0.956	0.947	0.953	0.953	0.929	0.937	0.913	0.937
<b>T<sub>eff</sub>/K<sup>(a)</sup></b>	358.4	371.2	417.3	447.4	478.3	513.7	539.8	568.7	586.3	636.1



**Figure S7.** Plots of “effective temperature”  $T_{eff}$  against CID energies.  $E_{cm}$ .



**Figure S8.** Plot of “Y-intercept” against “-Slope” values consigned in Table S7.

**Table S8.** Experimental proton affinity PA, protonation entropy  $\Delta_p S^0$  and basicity GB of paracetamol

PA. $\text{kJ}\cdot\text{mol}^{-1}$	$\Delta_p S^0$ . $\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$	GB. $\text{kJ}\cdot\text{mol}^{-1}$
$909.4 \pm 8.4$	$132.8 \pm 8.4$	$869.9 \pm 8.4$